ptr environmental services

Four Oaks Center • 1942 Oak Ridge Turnpike • Oak Ridge, Tennessee 37830 • 615/482-4337 • Telefax 615/482-4514

April 11, 1994

Ms. Diane Leber
Ciba-Geigy Corporation
444 Saw Mill River Road
Ardsley, NY 10502-2699

Dear Diane:

The purpose of this letter is to address preliminary media protection standards for polychlorinated dibenzo-p-dioxin/furan (PCDD/F) congeners associated with the production of Irgasan DP300. The four primary congeners associated with this product are:

- 2,8-Dichlorodibenzo-p-dioxin (2,8-DCDD)
- 1,3,7-Trichlorodibenzo-p-dioxin (1,3,7-TiCDD)
- 2,8-Dichlorodibenzofuran (2,8-DCDF)
- 2,4,8-Trichlorodibenzofuran (2,4,8-TiCDF)

Ciba conducted a series of toxicity tests on these four congeners. The results of these studies, along with their chemical structures, are summarized in the attached Ciba document. The studies were designed to evaluate the potential for causing chloracne, mutagenicity, and reproductive effects, all of which are toxic effects associated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD), and the other chlorinated dioxins/furans that are completely substituted at the 2,3,7, and 8 positions. No toxicity was demonstrated by the di- and tri-CDD/F congeners for the toxicity endpoints selected. These results are consistent with the peer-reviewed, published literature on the PCDD/Fs, showing that the toxicity is associated with higher chlorinated congeners, especially those with chlorine completely substituted at the 2,3,7, and 8 positions. Therefore, it is well-documented that the "super toxicity" of some of the PCDD/F congeners is extremely dependent on the chemical structure.

The USEPA (1989) and the international scientific community have developed a scheme of comparative toxicity for the PCDD/Fs that is based on the relative toxicity of each congener in a series of *in vitro* and *in vivo* biological test systems. The resulting consensus opinion is summarized in a table of toxicity equivalency factors (TEFs) which are proportional to the toxicity of each congener relative to 2,3,7,8-TCDD (congener of apparent highest toxicity).

All of the di- and tri- CDD/Fs are assigned a TEF of 0. The reasoning is that the di- and tri-CDD/Fs do not fit the highly characteristic toxicity pattern of a "wasting syndrome" of acute toxicity, specific receptor binding, and other specific enzyme systems induction in the liver and other body organs. Even octachlorodibenzo-p-dioxin/furan (OCDD/F), which have lower toxicity and the smallest TEF (0.001), in one study with male rats demonstrated many of these "dioxin-like" toxic effects after repeated dosing for 13 weeks.

Project No. 1.003.02

Since the di- and tri- CDD/Fs do not fit into the TEF scheme for comparative dioxin toxicity, an electronic database toxicity literature search was conducted on all of the di- and tri- CDD/F congeners. The literature available confirmed the low toxicity of these congeners. One study (Deml, et. al., 1989) showed aryl hydrocarbon hydroxylase (AHH) enzyme induction by 2,4,8-TiCDF at the lowest dose tested of 100 mg/kg/day. Apparently no other di- or tri- CDD/F was evaluated in this study. Using this study to estimate an oral reference dose (RfD_o) for people, the uncertainty factor approach is used as follows:

- 100 = uncertainty factor to extrapolate from an acute lowest-observed, adverse effect level to a chronic, no-observed, adverse effect level.
- 10 = uncertainty factor to extrapolate from rats to humans.
- 10 = uncertainty factor for human variability.
- Therefore, the overall uncertainty factor is 10,000, making the RfD_o 0.01 mg/kg/day for people.

Using this RfD_o and a residential exposure model, the following preliminary media protection standard is estimated:

$$C = \frac{(THI)\,(AT)}{(1/RfD_o)\,(CF)\,(EF)\,(IF)} \qquad (1)$$

where,

C	=	Soil concentration (mg/kg) for preliminary media protection standard
THI	=	Target hazard index = 1
RfD_o	=	Oral reference dose (mg/kg-d) = 0.01
AT	=	Averaging time (days; d) = 3285 (assumes 9 yr. at one residence)
CF	=	Conversion factor (10^{-6} kg/mg)
EF	=	Exposure frequency (d/yr) = 215
IF	=	Age-adjusted soil ingestion factor (mg/kg-d) = 34

C = 4,500 mg 2,4,8-TiCDF/kg soil

Another approach strictly for comparative purposes is to use the conclusion of Deml, et. al (1989) that 2,4,8-TiCDF was at least seven orders of magnitude less active than 2,3,7,8-TCDD in their studies. This implies that TiCDF is about 1×10^7 to 5×10^7 fold less toxic than 2,3,7,8-TCD. The latter compound has a cancer slope factor of 1.5×10^5 per mg/kg-day

(USEPA, 1994). If we were to assume that TiCDF is carcinogenic, which has not been demonstrated, the range for a slope factor would be 0.0006 to 0.003 per mg/kg-day. A preliminary media protection standard can be estimated using a residential exposure model as follows:

$$C = \frac{(TRL)\,(AT)}{(SF_o)\,(CF)\,(EF)\,(IF)} \qquad (2)$$

where:

C	=	Soil concentration (mg/kg) for preliminary media protection standard
TRL	=	Target risk level (unitless) = 10^{-5}
AT	=	Averaging time (days; d) = 25,550
SF_o	=	Oral cancer slope factor (per mg/kg-d) = 0.0006 to 0.003
CF	=	Conversion factor (10^{-6} kg/mg)
EF	=	Exposure frequency (d/yr.) = 215
IF	=	Age-adjusted soil ingestion factor (mg/kg-d) = 34

C = 2,300 to 11,500 mg 2,4,8-TiCDF/kg soil

The range given above brackets the 4,500 mg/kg result using the uncertainty factor approach. Again, it should be noted that these chlorinated di- and triCDD/Fs have not demonstrated carcinogenicity (USEPA, 1989). The 2,4,8-TiCDF soil concentration of 4,500 mg/kg appears to be an appropriate preliminary media protection standard for planning the next round of Phase 2 sampling.

The approach used in Equation 1 is taken to estimate an RfD_o for the di- and other tri- CDD/Fs using the Ciba studies. The repeated-dose study for teratogenicity in rats had a maximum dose of 3,000 mg/kg. No effect was demonstrated at this dose level for the teratogenicity endpoint. This is considered the key study, due to the multiple dosing scheme and the focus on reproductive toxicity, because this effect is associated with many of the CDD/Fs. The RfD_o is estimated as follows:

- 10 = uncertainty factor for the extrapolation of an acute no-observed adverse effect level to a chronic no-observed adverse effect level.

- 10 = uncertainty factor for extrapolating from rats to people.

- 10 = uncertainty factor for human variability.

- Therefore, 1,000 is the total uncertainty factor, making the RfD_o 3 mg/kg.

An Rfd_o of 3 mg/kg body weight/day for a 70-kg person translates into an oral daily exposure limit of 210 mg/d. An upper-bound estimate of soil ingestion for an adult is 100 mg of soil/day (200 mg/d for a child). Since the daily exposure limit for the di- and other tri- CDD/Fs exceeds the total amount of daily soil ingestion, it is obvious that ingestion of small amounts of these congeners with soil is not a concern for potential human health impacts.

Please call me if you have any questions about our approach to addressing preliminary media protection standards for these four PCDD/F congeners.

Sincerely,

Thomas C. Marshall.

Thomas C. Marshall, Ph.D., DABT
Principal

TCM/gn

References:

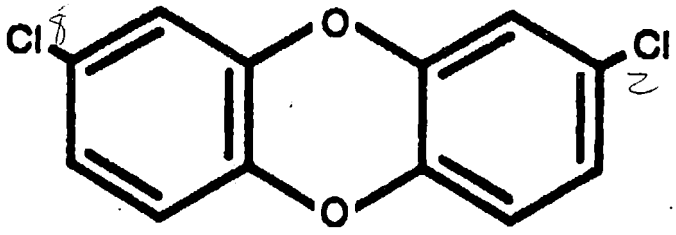
Deml, E., F.J. Wiebel and D. Oesterle, "Biological activity of 2,4,8-trichlorodibenzofuran: promotion of rate liver foci and induction of cytochrome P-450-dependent monooxygenases", *Toxicology*, 1989, 59: 229-238.

USEPA, 1989, "Interim Procedures for Estimating Risks Associated with Exposures to Mixtures of Chlorinated Dibenzo-p-Dioxins and Dibenzofurans (CDDs and CDFs) and 1989 Update," Prepared by the Risk Assessment Forum for the Office of Health and Environmental Assessment, Washington, DC, EPA/625/3-89/016, NTIS PB90-14765/AS.

USEPA, 1994, IRIS (Integrated Risk Information System), First Quarter Update. Environmental Criteria and Assessment Office, Cincinnati, OH.

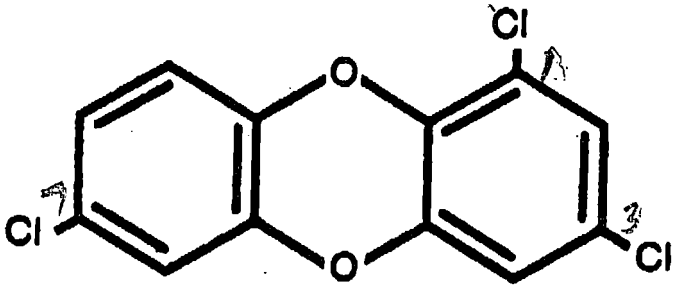
cc: M. Bernstein
F. Battaglia

Compound 1



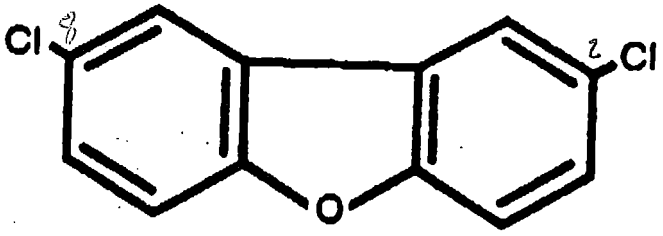
2,8-dichlorodibenzo-p-dioxin

Compound 2



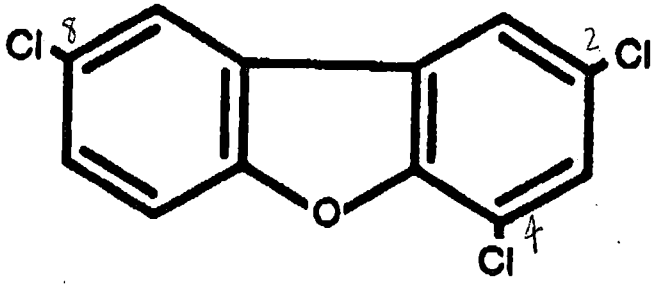
1,3,7-trichlorodibenzo-p-dioxin

Compound 3



2,8-dichlorodibenzofuran

Compound 4



2,4,8-trichlorodibenzofuran

Test	1	2	3	4
Oral LD_{50} (g/kg)	>5 (r)+ 8.47 (m)	>5 (r) >15 (m)	>15 (r,m)	>5 (r) >15 (m)
Chloracne	Neg.	Neg.	Neg.	Neg.
Dermal LD_{50} (g/kg)	>4 (r)	>4 (r)	-	-
Ames	Neg.	Neg.	Neg.	Neg.
Cytogenetics (Chinese Hamster)*	Neg.	Neg.	Neg.	Neg.
(Mouse)**	Neg.	Neg.	Neg.	Neg.
Dominant*** Lethal	Neg.	Neg.	Neg.	Neg.
Teratogenicity**** (Rat)	Neg.	Neg.	Neg.	Neg.

Footnotes:

r+ = rat, m = mouse

* bone marrow - dosages of 0.5, 1.0, and 2.0 g/kg

** spermatocytes - dosages up to 5.0 g/kg

** spermatogonia - dosages up to 2.5 g/kg

*** dosages up to 4.5 g/kg

**** dosages up to 3.0 g/kg